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TRANSMITTAL FORM (to be used for all correspondence after initial filing)	Application Number	08/846,658	
	Filing Date	May 1, 1997	
	First Named Inventor	John R. Adair et al.	
	Art Unit	1642	
	Examiner Name	Minh Tam B. Davis	
Total Number of Papers in This Submission	One	Attorney Docket Number	CARP0001-100

ENCLOSURES (check all that apply)

<input type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment / Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Reply to Missing Parts/ Incomplete Application <input type="checkbox"/> Reply to Missing Parts under 37 CFR1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____ <input type="checkbox"/> Landscape Table on CD	<input type="checkbox"/> After Allowance Communication to TC <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input checked="" type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): - Claims Appendix - Evidence Appendix - Related Proceedings Appendix - None
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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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Date	September 8, 2006	Reg. No.	35,719

CERTIFICATE OF TRANSMISSION/MAILING

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This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: Adair et al.
Serial No.: 08/846,658
Filing Date: May 1, 1997
For: HUMANISED ANTIBODIES
Customer No.: 34132

Confirmation No. 9631
Art Unit No.: 1642
Examiner: Minh Tam B. Davis
Docket No.: CARP0001-100

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DATE OF DEPOSIT: September 8, 2006

MAIL STOP APPEAL BRIEF- PATENTS

Commissioner for Patents
P.O. Box 1450
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Dear Sir: /

APPEAL BRIEF UNDER 37 CFR § 41.37

This Appeal Brief is being filed in response to the Notice of Non-Compliant Appeal Brief under 37 CFR § 41.37 dated August 24, 2006 ("Notice"). The Notice alleges that Appellants' Appeal Brief filed June 2, 2006, was non-compliant for containing arguments regarding the references cited on pages 1-3 of the Appeal Brief, which should have been presented in the "Argument" section of the Appeal Brief. This error has been corrected in the present Appeal Brief. It is Applicants' belief that no extension or fee is necessary. If this belief is in error, Applicants hereby request the appropriate extension of time and authorize the Office to charge any fee to Deposit Account 50-1275.

This is an appeal from the Office Action dated as mailed May 2, 2005 ("present Office Action"), rejecting claims 24-31 in the above-identified application. A Notice of Appeal was filed November 2, 2005. A petition for a five-month extension of time and the appropriate fee

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accompanied the Appeal Brief filed June 2, 2006. Pursuant to MPEP §1207.4, Appellants requested that the brief fee of \$500.00 previous paid on February 14, 2005, be applied to this Appeal Brief.

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REAL PARTY IN INTEREST

The real party in interest is UCB S.A. A document evidencing the same will be recorded in due course. The previous real party in interest was Celltech R & D, Ltd. (formerly Celltech Therapeutics, Limited).

RELATED APPEALS AND INTERFERENCES

An Appeal Brief was filed on July 17, 2006, in Application Serial No. 08/485,686, filed June 7, 1995, which claims priority to the same applications as the present application, i.e., Application Serial Nos. 08/303,565, 07/743,329, and GB Application No. 8938874. There are no other appeals or interferences which will directly affect, will be directly affected by, or have a bearing on the Board's decision in the present appeal.

STATUS OF CLAIMS

The claims pending in this application are Claims 24-31. All claims stand rejected. The pending claims are appended hereto in the Claims Appendix.

STATUS OF AMENDMENTS

All amendments have been entered.

SUMMARY OF CLAIMED SUBJECT MATTER

Humanised immunoglobulins are, usually, derived from monoclonal antibodies generated in rodents (mice) that have been genetically engineered to appear more human. The development of monoclonal antibody technology in the late 1970s enabled the preparation of homogeneous antibody populations directed to a single, specific target (page 2, lines 1-3). These "magic bullets," as they are often referred to, had great therapeutic potential. They also had one major drawback – they were generally prepared from mouse sources and administration to humans resulted in a human anti-mouse antibody ("HAMA") response which greatly impaired

their effectiveness (page 2, lines 8-29). With the concomitant development of recombinant DNA technology, artisans were able to prepare antibodies that had the binding capabilities of the mouse monoclonal antibodies yet looked more like human antibodies and, thus, exhibited a decreased HAMA response.

As described in the present specification, early attempts to decrease the HAMA response focused upon matching the entire variable region of the antibody chains, i.e., the region that binds to antigen (page 3, lines 4-16), to the mouse monoclonal antibody. There was still a significant risk of HAMA response (page 3, lines 16-21). Subsequent attempts matched only what are referred to as the Complementarity Determining Regions (“CDRs”) of the variable regions (page 3, lines 22-29) to the mouse monoclonal antibody. These are the regions that are most variable and believed to be responsible for the binding of antigen. Matching of these regions alone, however, was not satisfactory; the binding to antigen was often just a fraction of that of the original monoclonal antibody (page 4, lines 10-14). It was subsequently discovered that having residues match the mouse monoclonal residues in the variable region in addition to the CDRs, i.e., in the framework region, achieved satisfactory binding while minimizing the HAMA response. Initially, two residues outside the CDRs as defined by Kabat et al (Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services, NIH, USA, 1987, reference 7 cited on page 65 of the specification), **but within** the structural loops, were also matched to the mouse monoclonal residues, with a resultant improvement in binding over the matching of the CDRs alone (page 4, lines 14-24). The present invention is directed to antibodies having residues **outside** the CDRs as defined by Kabat **and** the structural loops that match the mouse monoclonal residues. The Kabat CDRs completely encompass the structural loops except for the first CDR of the heavy chain. The structural loop for this CDR extends from

residues 26-32 (page 19, lines 28-29); the Kabat CDR extends from residues 31-35 (page 19, line 23).

The claims of the present application are directed to such humanised immunoglobulins. Support for the limitations of independent claims 24 and 28 in the application as filed is presented in the table below.

24. A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chains	Page 1, lines 5-16, and page 7, line 32, through page 8, line 21.
which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least 10^8 M^{-1} .	Page 11, lines 27-30.
wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside both the Kabat CDRs and the structural loop CDRs of the variable regions,	Page 6, lines 14-23, page 8, lines 13-16, and page 19, line 16, to page 20, line 15.
wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks,	Page 6, line 12, to page 7, line 5.
and each of said donor amino acids contributes to antigen binding as determined by X-ray crystallography.	Page 38, lines 1-12, and lines 23-38, and Figs. 3-4 of the application as filed reference residues that may “contribute to antigen binding” as determined using X-ray crystallography. Residues 48, 49, 71, 73, 76, 78, 88, and 91 are so identified in Figure 4.
28. A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chains	Page 1, lines 5-16, and page 7, line 32, through page 8, line 21.

which humanized immunoglobulin specifically binds to an antigen with an effective antigen binding affinity	Page 11, lines 23-30 and page 37, lines 5-10.
wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside both the Kabat CDRs and the structural loop CDRs of the variable regions,	Page 6, lines 14-23, page 8, lines 13-16, and page 19, line 16, to page 20, line 15.
wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks,	Page 6, line 12, to page 7, line 5.
and each of said donor amino acids contributes to antigen binding as determined by X-ray crystallography.	Page 38, lines 1-12, and lines 23-38, and Figs. 3-4 of the application as filed reference residues that may “contribute to antigen binding” as determined using X-ray crystallography. Residues 48, 49, 71, 73, 76, 78, 88, and 91 are so identified in Figure 4.

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

There is one ground of rejection presented for review. The ground of rejection is the rejection of all pending claims under 35 U.S.C. § 102(e), or in the alternative, under 35 U.S.C. § 103, (see Office Action) over the Queen patent, U.S. Patent No. 5,585,089.

ARGUMENT

Before addressing the ground of rejection, Appellants wish to address the Office’s actions in this application necessitating the re-filing of an Appeal Brief. An Appeal Brief was previously filed in this application on February 14, 2005. In response, the Office reopened prosecution and levied the present Office Action. The alleged basis for the reopening of prosecution was to “include art not previously cited.” (See page 2 of the present Office Action.) Although the Office did not specify a new rejection, it appears that the previous rejection under 35 U.S.C. §102(e) over U.S. Patent No. 5,585,089 (“the Queen patent”) was expanded to be under 35

U.S.C. §103 as well. The allegedly new art was not cited as a basis for the rejection but, rather, was relied upon in the body of the present Office Action. Both of the references cited, however, are cumulative.

Winter et al, US 6,548,640 B1, was cited for the discussion that the hypervariable regions are similar by either sequence or structural criterion, except for the first hypervariable loop of the heavy chain. This information is presented in the primary reference, i.e., the Queen patent, and is, thus, cumulative. See col. 15, lines 43-45, of the Queen patent:

Chothia and Lesk (op. cit.) define the CDRs differently from Kabat et al. (op. cit.). Notably, CDR1 is defined as including residues 26-32.

Both Chothia and Lesk and Kabat et al. are incorporated by reference in the Queen patent. See col. 11, lines 41-44 and col. 15, lines 24-27, of the Queen patent.

The other reference, Lohmeyer J et al, was purportedly relied upon as motivation for producing antibodies to CD3 and CD4. Both antigens, however, have been recited in the claims since the present application was first filed, i.e., **May 1, 1997**. That the Office is just now getting around to citing such a reference is unfathomable, particularly considering that this is the **third** search performed by the Office in this application's eight-year plus history. If the previous searches had been performed as proscribed (see MPEP 904.02), one would have expected this reference to have been identified years ago. That the Office is now using this reference as a basis to reopen prosecution is simply untenable.

Regardless, this reference is also cumulative. Both antigens are identified in First International Leukocyte Differentiation Workshop, Leukocyte Typing, Bernard et al., Eds., Springer-Verlag, N.Y. (1984) which, as the Office acknowledged in the present Office Action, is

incorporated by reference in the Queen patent in a discussion of antibodies to be humanized according to the invention (see the Queen patent, col. 19, lines 32-40).

Under the circumstances, Appellants believe that the reopening of prosecution in this application is inappropriate at best, dilatory at worst. Appellants submit that the Office's actions are contrary to its own procedures. According to MPEP 707.02, any application that has been pending **five** years, **or** which is up for the **third or subsequent** action, should be carefully studied by the supervisory patent examiner and every effort should be made to finally conclude prosecution. This application has been pending for over **eight** years, and this is the **seventh** official action (see Image File Wrapper). The Office, however, does not seem to be making every effort to finally conclude prosecution. Rather, the Office appears to be facilitating the further protraction of prosecution.

Nonetheless, in response to the present Office Action, and pursuant to MPEP 1207.04, Appellants are filing this Appeal Brief. As the appendices have not changed from the Appeal Brief filed on February 14, 2005, and a review of PAIR indicates that the entire Appeal Brief filed on February 14, 2005 and all its appendices are in the Image File Wrapper, Appellants herein request that the Office refer to the previously filed evidence appendices referred to as attached herein and not require Appellants to resubmit the same, particularly considering that there are over 250 pages of appendices. Appellants note that the requirement for the filing of a complete new appeal brief is not proscribed by statute, nor regulation.

Claims 24-31 are not anticipated by, or obvious over, the Queen patent (U.S. Patent No. 5,585,089)

Appellants are attempting to provoke an interference with the Queen patent. One ground of rejection of the presently pending claims, i.e., claims 24-31, remains. Claims 24-31 are

rejected under 35 U.S.C. § 102(e)/103 as allegedly anticipated by or obvious over the Queen patent. For the reasons discussed in more detail below, Appellants maintain that the Queen patent is not an appropriate reference under 35 U.S.C. § 102(e)/103. The Queen patent is not entitled to an effective filing date earlier than Appellants' effective filing date of **December 21, 1989**.

Appellants maintain that the Queen patent is not entitled to the priority dates of its two earliest priority applications filed December 28, 1988 and February 13, 1989, respectively. The next earliest priority date for the Queen patent is **September 28, 1990**, which is after Appellants' effective filing date of December 21, 1989. Because the Queen patent is not entitled to its two earliest priority dates, it is not an appropriate reference under 35 U.S.C. § 102(e)/103.

As has been repeatedly advanced by Appellants during prosecution of the present application, the Queen patent contains several continuation-in-part applications in its priority chain. As has also been repeatedly advanced by Appellants during prosecution of the present application, when the priority chain contains an application that is a continuation-in-part of the parent application

in order to carry back the 35 U.S.C. 102(e) critical date of the U.S. patent reference to the filing date of a parent application, the ****>U.S. patent reference< must *** have a right of priority to the earlier date under 35 U.S.C. 120 or 365(c) and ***>the parent application must<** support the invention **claimed** as required by 35 U.S.C. 112, first paragraph. "For if a patent could not theoretically have issued the day the application was filed, it is not entitled to be used against another as 'secret prior art' under

35 U.S.C. 102(e).” *In re Wertheim*, 646 F.2d 527, 537, 209 USPQ 554, 564 (CCPA 1981).

(MPEP 2163.03, IV, emphasis in bold added.) 35 U.S.C. §112, first paragraph, provides that

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . .

(35 U.S.C. §112, first paragraph.) “Section 112 requires that the application **describe**, enable, and set forth the best mode of carrying out the invention.” *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 724, 62 USPQ2d 1705, 1707 (2002) (emphasis added).

Appellants maintain that the issued claims of the Queen patent are not entitled to the filing dates of, at least, the two earliest priority applications because there is no written descriptive support for several of the claim limitations in those applications.¹

The Queen patent is attached as Evidence Appendix A. Each one of the claims of the Queen patent contain the following limitations that Appellants have maintained do not find support in, at least, the two earliest priority documents:

1. “an affinity constant of at least 10^7 M^{-1} ,”
2. “no greater than about four-fold that of the donor immunoglobulin;” and
3. “outside the Kabat and Chothia CDRs.”

¹ If the Office is delaying prosecution with the hope that certain proposed legislation would effectively overrule *Wertheim*, such a tactic appears futile. Even if the proposed legislation becomes law in the near future, it would not apply to the Queen patent – the legislation, as proposed, only applies to patents issued on applications having claims having an effective filing date one year or more **after** the date of enactment.

See, for example, the Request for Reconsideration filed on May 24, 2000 (“May 2000 Request,” copy attached as Evidence Appendix B). The May 2000 Request includes a chart appended thereto as Appendix A identifying, *inter alia*, the foregoing limitations of the Queen patent and setting forth the reasons why they do not find support in the two earliest priority applications. Although most of the exchanges with the Patent Office subsequent to the filing of the May 2000 Request focused upon the last limitation listed above, Appellants have also argued lack of support for the first two limitations.

In the answer to Appellants arguments designated as “A” in the present Office Action, the Office dismissed the first and second limitations listed above as not germane to Appellants’ claims because they are not found in Appellants’ claims and, therefore, the Office only addressed arguments related to the third limitation. The Office’s dismissal reflects a clear misunderstanding of Appellants’ arguments and of the law. These limitations are present in the **issued claims** of the **Queen patent**. Accordingly, for the Queen patent to be entitled to the two earliest priority dates as a reference under 35 USC §102(e)/103, these limitations must be supported in those priority documents. *See Wertheim*, 646 F.2d 527, 537, 209 USPQ 554, 564. Appellants are arguing that there is no support for these limitations in the priority documents of the Queen patent and, thus, the Queen patent is not entitled to these earlier priority dates as a reference under 35 USC § 102(e)/103). The Office’s misapplication of the law on this point is disconcerting.

Addressing each limitation in turn, the recitation of “an affinity constant of at least 10^7 M^{-1} ” is clearly not present in the two earliest priority applications. These applications recite, rather, that the affinity constant is “**stronger** than about 10^8 M^{-1} ” (*see* page 4, line 36, of Application Serial No. 07/310,252, “the 252 application,” Evidence Appendix C and page 4, line 25 of

Application Serial No. 07/290,975, “the 975 application,” Evidence Appendix D, emphasis added) and “at least about 10^8 M^{-1} , preferably 10^9 M^{-1} to 10^{10} M^{-1} , or stronger” (see page 7, lines 13-14 of the 252 application, Evidence Appendix C and page 8, lines 4-5 of the 975 application, Evidence Appendix D). Claim 13 of the 252 application and claim 5 of the 975 application recite that the affinity be “about 10^8 M^{-1} or stronger” (see Evidence Appendix C and Evidence Appendix D, respectively). Claim 12 of the 975 application recites that the affinity is “at least about 10^8 M^{-1} ” (see Evidence Appendix D). There is no recitation of an affinity constant of “at least 10^7 M^{-1} ” in these applications.

Nor can it be said that such a recitation is implicit or inherent. The passages cited above are clearly setting a floor for affinity of “about” or “at least about” 10^8 M^{-1} ; the actual affinities are to be greater than this value. The limitation “ 10^7 M^{-1} ,” however, is **not** greater than 10^8 M^{-1} ; it is less. To the extent it can be argued that the recitation of “about” or “at least about” lowers this floor somewhat, it certainly cannot be said that it lowers it 10-fold to include “at least 10^7 M^{-1} .” See *Pieczenik v. Dyax Corp.*, 226 F. Supp. 2d 314, 321 (D.C. Mass. 2002), which stated that:

[i]n similar fashion, in the interest of lexicographic consistency, “at least about 10%” can be understood to perhaps capture 9%, or given the qualification of “at least about 10%,” perhaps a number substantially above 10%, but certainly not 1%, as plaintiffs’ expert, Dr. Makowski, maintains.

Nor is it sufficient, as the Office alleges on page 8 of the present Office Action, that the disclosed binding affinities are “within the range of the claimed binding affinity.” Appellants’ argument is that the range itself, more particularly the lower limit thereof, is

not disclosed. The disclosure of a single point within a range, although sufficient to anticipate a range, does not disclose the range itself. The range could be anything; it could be broad, narrow, or infinite.

Appellants maintain that there is no written descriptive support for the limitation “at least 10^7 M^{-1} ” in the two earliest priority applications of the Queen patent.

The second limitation listed above, i.e., “no greater than about four-fold that of the donor immunoglobulin,” is also not supported by the two earliest priority applications (*see* chart appended to Evidence Appendix B). This limitation requires that the affinity level should not be four-fold greater than that of the donor. As should be apparent from the discussion in the “Summary of Claimed Subject Matter” herein, the concern was not that the affinity levels of the humanized antibodies would be **greater** than that of the donor immunoglobulin but, rather, that the affinity levels would be much **less** than that of the donor immunoglobulin. Consistent therewith, the 252 application recited that the affinity level be “**within** about 4 fold of the donor immunoglobulin’s original affinity to the antigen” (page 4, lines 35-37, of the 252 application, Evidence Appendix C, *emphasis added*), suggesting that the affinity level should not be more than four-fold **less** than that of the donor. A review of the 252 application confirms this interpretation. See, for example, the discussion on page 10, lines 7-10, of the 252 application, Evidence Appendix C:

The present invention is based in part on the model that two contributing causes of the **loss** of affinity in prior means of producing humanized antibodies (using as examples mouse antibodies as the source of CDRs) are . . .

Id. (emphasis added). Appellants identified no discussion of this limitation in the 975 application.

Nor can it be said that this recitation is implicit or inherent in either of the priority applications. This recitation is contrary to the expectation in the art for humanized antibodies as compared with the donor antibodies, i.e., a lower affinity. Applicants maintain that there is no written descriptive support for the limitation “no greater than about four-fold that of the donor immunoglobulin” in the two earliest priority applications of the Queen patent.

Finally, as Appellants argued in the Preliminary Amendment filed May 1, 1997 with the present application, and have consistently argued thereafter, the limitation “outside the Kabat and Chothia CDRs” is also not supported by either of the two earliest priority applications. This limitation **requires** that there be changes to donor amino acids in the framework region outside **both** the Kabat and Chothia CDRs. The priority applications did not require that the changes to donor be outside the Chothia CDR.

This limitation was added to the claims in a preliminary amendment in the application that issued as the Queen patent (filed June 7, 1995) and, indeed, was necessary to secure allowance of the Queen patent claims over the prior art. During prosecution of the Queen patent, the Riechmann reference, *inter alia*, was cited to support an obviousness rejection. (See Paper No. 7, Application Serial No. 07/634,278, filed December 19, 1990, attached as Exhibit 6 to the Supplemental Amendment filed in the present application on March 17, 2003, hereinafter “Supplemental Amendment,” page 7, attached hereto as Evidence Appendix E.) The Riechmann reference discloses an antibody in which the CDRs (as defined by Kabat) and, additionally, residue 27 alone or residues 27 and 30 combined are changed to donor. The claims being prosecuted at the time the rejection was levied recited that the CDRs “and **at least one** residue

immediately adjacent to at least one of said CDRs are from different immunoglobulin molecules than the framework regions.” (Paper No. 6, Application Serial No. 07/634,278, filed December 19, 1990, attached as Exhibit 5 to the Supplemental Amendment filed in the present application on March 17, 2003, page 1, emphasis added, attached hereto as Evidence Appendix F.)

As discussed above, the extents of the Kabat CDRs and the Chothia hypervariable loops (hereinafter “Chothia CDRs”)² are not the same. For example, for the heavy chain, the first Kabat CDR comprises residues 31-35 (*see* page 19, lines 15-23, of the present application as filed); the first heavy chain Chothia CDR, however, comprises residues 26-32 (*see* page 19, lines 24-30, of the present application as filed). Residue 30, disclosed to be changed to donor in the Riechmann reference, is **immediately adjacent** to the first **Kabat** CDR for the heavy chain, but **within** the first **Chothia** CDR for the heavy chain. Riechmann, thus, read on the limitation that “at least one residue immediately adjacent to at least one of said CDRs are from different immunoglobulin molecules than the framework regions.” To overcome the rejection over Riechmann, Queen ultimately added the limitation that the residue to be changed to donor must be outside the Kabat **and** Chothia CDRs. This limitation was added in a preliminary amendment that accompanied the filing of the application which issued as the Queen patent. The rejection was not applied thereafter.

In the answer to Appellants’ Arguments designated as “B” in the present Office Action, the Office alleged that Queen’s arguments (presumably the Office meant actions here) in Application Serial No. 07/634,278 are not germane, because each case is decided on its own facts and, allegedly, it is well settled that whether **similar** claims have been allowed to **others** is

² Although the Chothia reference, discussed *infra*, does not call the regions CDRs, but rather hypervariable loops, Appellants are using the patentees’ nomenclature for ease of discussion.

immaterial. The relevant action was not taken in the prior application, however, but in the application that issued as the Queen patent. Even if the actions taken were in the prior application, it is part of the same prosecution history. The prosecution history of a prior patent has been held to be relevant to the interpretation of a common term in a second patent stemming from the same parent application. *See Microsoft Corp. v. Multi-Tech Systems, Inc.*, 357 F.3d 1340, 1349, 69 USPQ2D 1815, 1823 (Fed. Cir. 2004), citing *Jonsson v. Stanley Works*, 903 F.2d 812, 818, 14 USPQ2d 1863, 1869 (Fed. Cir. 1990). Application Serial No. 07/634,278 itself issued as a patent.

As noted previously, the two earliest priority applications of the Queen patent did not require that there be changes to donor in the framework outside both the Kabat **and** Chothia CDRs. Rather, they described either a single change to donor anywhere in the framework, including residues within the first Chothia heavy chain CDR, i.e., residues 26-32 or, even, no change to donor in the framework. See, for example, claims 8 and 17 and page 21, lines 23-29 – suggesting that residues 27 and 30 be changed to donor, both of which are within the first heavy chain Chothia CDR -- of the 252 application (Evidence Appendix C), and page 21, lines 23-30 of the 975 application – suggesting that residues 27 and 30 be changed to donor, both of which are within the first heavy chain Chothia CDR (Evidence Appendix D). Indeed, the 975 application, which was directed to a specific antibody, contemplated just matching the CDRs (*see* page 8, lines 7-11 of Evidence Appendix D).

Nonetheless, throughout prosecution of the present application, the Office has endeavored to find support for this limitation in the two earliest priority applications. Initially, the Office simply cited to allegedly supporting text in the priority applications without advancing any argument as to why the text supported the limitation. See, for example, the Final Rejection

dated as mailed May 28, 1999 ("May 1999 Action"). In the May 1999 Action, the Office argued that the limitation was taught on page 9, lines 1-5, of the 975 application and page 13, lines 1-18 of the 252 application. As Appellants argued in the response thereto, neither passage cited supports the Office's contention.

The passage on page 9, lines 1-5, of the 975 application (Evidence Appendix D), contains a background discussion of the hypervariable regions, which it reports are also called CDRs. References by Kabat and Chothia are cited, and incorporated by reference. This passage is the only one in the 975 application linking Chothia to the term "CDRs." Other passages specifically referring to the CDRs make it clear that the CDRs are as defined by Kabat. For example, on page 10, line 2, of the 975 application (Evidence Appendix D), the framework regions are defined in terms of Kabat. If the framework regions are defined in terms of Kabat, the CDRs must be as well. On page 21 of the 975 application (Evidence Appendix D), the protocol for selecting which residues in the heavy chain are to be donor is set out. At lines 19-22, residues which fall in positions within a CDR **"as defined by Kabat, [i.e.,] amino acids 31-35 . . ."** are specified to be donor. At lines 28-30, amino acid 30 is listed as a position **immediately adjacent to a CDR** to be changed to donor. Amino acid 30 is adjacent to the first Kabat heavy chain CDR, but **within** the first Chothia heavy chain CDR. The description of Figure 1 of the 975 application indicates that it refers to the heavy chains and that the three CDRs are underlined (page 6, lines 1-6, Evidence Appendix D). In Figure 1, only amino acids 31-35 are underlined for the first heavy chain CDR.

Neither is there support for this limitation in the other passage relied upon by the Office, i.e., page 13, lines 1-18 of the 252 application. The reference to Chothia in this passage is in the context of computer programs for computer modeling of antibodies. There is no reference to

CDRs. Contrastingly, the specific references to CDRs in the 252 application make it clear that the CDRs are as defined by Kabat. On page 8, lines 22-26, the 252 application (Evidence Appendix C) reports that the extents of the framework region and CDRs have been “precisely defined” by Kabat. On page 21, of the 252 application (Evidence Appendix C), the protocol for selecting which residues in the heavy chain are to be donor is set out. At lines 20-22, residues which fall in positions within a CDR **“as defined by Kabat, [i.e.,] amino acids 31-35 . . .”** are specified to be donor. At lines 27-29, amino acid 30 is listed as a position **immediately adjacent to a CDR** to be changed to donor (emphasis added). Amino acid 30 is adjacent to the first Kabat heavy chain CDR, but **within** the first Chothia heavy chain CDR. The description of Figure 1 of the 252 application indicates that it refers to the heavy chains and that the three CDRs are underlined (page 5, lines 13-20). In Figure 1, only amino acids 31-35 of the first heavy chain CDR are underlined. As is clear from the foregoing, all specific references to CDRs in both the 252 application and the 975 application are to Kabat CDRs.

The first time the Office advanced any argument as to why the passages cited in the 975 application and the 252 application supported its interpretation was in an Advisory Action dated as mailed July 31, 2001 (“July 2001 Action”). Rather than argue that the two priority applications supported the limitation “outside the Kabat and Chothia CDRs,” the Office asserted that one of ordinary skill, based on the 975 specification, would have recognized that CDRs as taught by the Queen patent would **include** CDRs as defined by Chothia, regardless what the rest of the specification discloses as examples of Kabat CDRs. Presumably, in the Office’s view, if the specification supported an interpretation of CDRs to mean Kabat and Chothia, the issue for support of the limitation “outside the Kabat and Chothia CDRs” was resolved. This interpretation of the term “CDRs” as found in the claims of the Queen patent, however, is

inconsistent with the claims, specification, and file history of the Queen patent, much less, as discussed above, the two earliest priority documents. As the Court of Appeals for the Federal Circuit has consistently held:

In determining the meaning of disputed claim language, a court looks first to the intrinsic evidence of record, examining, in order, the claim language itself, the specification, and the prosecution history.

Alza Corp. v. Mylan Laboratories Inc., 391 F.3d 1365, 1370, 73 USPQ2d 1161, 1164 (Fed. Cir. 2004), citing *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331, 59 USPQ2d 1401, 1407 (Fed. Cir. 2001) (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582, 39 USPQ2d 1573, 1576 (Fed. Cir. 1996)). The import of intrinsic evidence is reiterated in *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005), *en banc*.

Claim 1 of the Queen patent is duplicated below:

1. A humanized immunoglobulin having **complementarity determining regions (CDRs)** from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least 10^7 M^{-1} and no greater than about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework **outside the Kabat and Chothia CDRs**, wherein the donor amino acids replace

corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, and each of said donor amino acids:

- (I) is adjacent to a CDR in the donor immunoglobulin sequence or
- (II) contains an atom within a distance of 4 Å of a CDR in said humanized immunoglobulin.

(The Queen patent, claim 1, Evidence Appendix A, emphasis added.) The first limitation of claim 1 does not recite “Kabat and Chothia CDRs” but, merely, “CDRs.” Further, the specification of the Queen patent does not define the term “CDRs” as meaning Kabat and Chothia. The specification defines CDRs in terms of Kabat. For example, the general protocol set forth at column 14 of the Queen patent, listing the categories of what amino acids may be selected as donor, defines CDRs in terms of Kabat :

Category 1: The amino acid position is in a CDR is [sic] defined by Kabat et al., op. cit.

(see col. 14, lines 1-2, of the Queen patent, Evidence Appendix A.) Consistent therewith, all the examples in the Queen patent list residues 31-35 as the residues for the first CDR of the heavy chain (see Tables 1, 4, 6, 7, 8, and 9 of the Queen patent, Evidence Appendix A). As discussed above, the first heavy chain Kabat CDR comprises residues 31-35; the first heavy chain CDR of Chothia comprises residues 26-32.

Further, as Appellants pointed out previously during prosecution, such an interpretation would make the recitation “outside the Kabat and Chothia CDRs” superfluous. But, as Appellants also argued, the prosecution history for the Queen patent indicates that this recitation

was necessary to secure allowance. Indeed, when faced with a rejection over Riechmann, Queen did **not** argue that “CDR” means Kabat plus Chothia. Queen, rather, added the “outside the Kabat and Chothia CDRs” limitation in the application that issued as the Queen patent. (*See* the Supplemental Amendment, Evidence Appendix L.) As Appellants also argued in the Supplemental Amendment, Queen submitted a glossary during prosecution of the application that issued as the Queen patent which stated that two distinct definitions of CDRs are in use – Kabat and Chothia. The Office’s interpretation, thus, is not supported by the Queen file history.

Additionally, as is clear from the discussion of the two earliest priority documents above, all specific references to CDRs were to Kabat CDRs, not Kabat and Chothia. Accordingly, even if the Office’s interpretation were correct, the two earliest priority documents do not support the Office’s interpretation.

Finally, as Appellants argued previously, the Office’s interpretation was not only contrary to the intrinsic record (as set forth above), it was also contrary to what Queen had argued during prosecution of the European equivalent applications of the Queen patent when faced with rejections/objections similar to the written description requirement of 35 U.S.C. § 112, first paragraph. Notably, the European equivalent applications claimed priority to the 975 application and the 252 application.

In Queen’s European patent 451,216 (“the European patent”), granted claim 1 recited that there was to be “at least one amino acid substitution outside of” CDRs “as defined by Kabat et al . . . together with Chothia et al . . .” (copy attached as Exhibit 1 to the Request for Reconsideration filed May 20, 2002, attached hereto as Evidence Appendix G). The European patent was revoked in its entirety under Article 123(2) of the European Patent Convention, which

was set forth in the Request for Reconsideration filed May 20, 2002 (Evidence Appendix H) and is duplicated below:

A European patent application or a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

The European Board of Opposition (“European Board”) concluded that

the feature *Kabat [...]together with Chothia [...]*” in claim 1 has neither a technically reasonable nor a legal basis in the application documents as filed; claim 1 does not therefore meet the requirements of Art. 123(2) EPC.

(See Interlocutory decision in Opposition Proceedings, page 27, copy enclosed with the Request for Reconsideration filed May 20, 2002, as Exhibit 4, attached hereto as Evidence Appendix I.) Again, the European patent claimed priority to the 975 application and the 252 application. The European Board also interpreted the reference merely to “CDRs” in granted claim 7 of the European patent, without further definition, to mean Kabat and Chothia CDRs and, thus, revoked it as well. *Id.*

In an appeal of the decision revoking the patent, Queen submitted claims similar to granted claim 7, i.e., referencing merely “CDRs.” Queen argued that, contrary to the finding of the European Board,

. . . unless specifically defining CDR’s otherwise as done in granted claim 1, the person skilled in the art when reading the application **as filed** and the patent specification would have

inevitably understood that the CDRs in granted claim 7 referred to Kabat CDRs.

(See paper filed June 22, 2001 by Protein Design Labs in appeal of EP-B1 0451 216, page 8, copy attached to the Request for Reconsideration filed May 20, 2002, as Exhibit 5, attached hereto as Evidence Appendix J, emphasis added.) Again, the European patent claimed priority to the 975 application and the 252 application.

Indeed, in a paper filed in a separate action, i.e., the opposition of a divisional application stemming from the application that issued as the European patent, Queen further argued that

. . . **nowhere** does the contested Patent state that the Chothia definition is to be used in **carrying** out the invention or in **understanding** the claims.

(See paper filed July 13, 2001 by Protein Design Labs in EP 95 10 5609.2, page 6, copy attached to the Request for Reconsideration filed May 20, 2002 as Exhibit 6, attached hereto as Evidence Appendix K, emphasis added.) Appellants maintained that the Office's position that the term "CDRs" included the Kabat and Chothia CDRs was not only inapposite to the intrinsic record but, also, was inapposite to the interpretation Queen advanced in another forum when faced with a rejection similar to lack of written description for a similar claim term.

In a Final Rejection dated as mailed December 18, 2001, the Office argued that the last-cited passage above was not relevant to the specification of the 975 application since it clearly seemed to refer to the added passage in the European patent. The Office had apparently overlooked the fact that the added passage was objectionable precisely because there was no support for it in the very same two priority applications which Appellants contend do not support a similar recitation. The Office was reminded of this in a response filed December 23, 2002, with

a Request for Continued Examination. Nonetheless, in the Office Action that followed that response, dated as mailed March 26, 2003 (“March 2003 Action”), the Office maintained the position that CDRs meant Kabat plus Chothia.

In the interim, the Supplemental Amendment discussed above had been filed by Appellants on March 17, 2003, which had not been received prior to the March 2003 Action. In the Office Action that followed the Supplemental Amendment, dated as mailed August 21, 2003 (“August 2003 Action”), the Office now **changed** its position and, quite surprisingly, argued that Appellants had misquoted the examiner’s previous position. The Office stated that

The Examiner did not state that CDRs means Kabat “plus” Chothia. Rather, the Examiner position is that CDRs, as incorporated by reference by Queen et al in the ‘975 specification could mean **either** the CDR amino acids defined by Kabat, **or** the amino acids in the hypervariable region taught by Chothia et al (The hypervariable regions are also called CDR’s [sic] according to Queen et al, in 07/290975 application, p. 8, last paragraph, bridging p.9).

(See August 2003 Action, sentence bridging pages 3-4, *et. seq.*, emphasis added.) In the immediately prior Office Action, however, the Office had asserted that

one of ordinary skill in the art would have recognized that CDRs as taught by Queen et al would **include also** CDRs as defined by Chothia et al, besides CDRs as defined by Kabat et al, regardless of whether the rest of the specification discloses as examples Kabat’s CDR’s.

(See March 2003 Action, page 4, emphasis added.) And, as referenced above, a similar statement had been made in the July 2001 Action. These statements would seem to support Appellants' interpretation of the Office's prior position, particularly considering that the passage Appellants were arguing was not supported was "outside the Kabat **and** Chothia CDRs." Regardless, the intrinsic record of the Queen patent does not support the Office's latter interpretation of CDRs either.

The first limitation of claim 1 of the Queen patent does not recite "Kabat or Chothia CDRs," but merely "CDRs." (See the Queen patent, claim 1, Evidence Appendix A, emphasis added.) Further, the specification of the Queen patent does not define the term "CDRs" as meaning Kabat **or** Chothia. Again, the general protocol set forth at column 14 of the Queen patent listing the categories of what amino acids may be selected as donor defines CDRs in terms of Kabat :

Category 1: The amino acid position is in a CDR is [sic] defined by Kabat et al., op. cit.

(see col. 14, lines 1-2, of the Queen patent, Evidence Appendix A.) And, all the examples in the Queen patent list residues 31-35 as the residues for the first CDR of the heavy chain (see Tables 1, 4, 6, 7, 8, and 9 of the Queen patent, Evidence Appendix A). And, as discussed above, the first heavy chain Kabat CDR comprises residues 31-35; the first heavy chain CDR of Chothia comprises residues 26-32. An interpretation as advanced by the Office, thus, would render the claims indefinite. Depending upon which CDR is contemplated, a product may or may not infringe. Further, one cannot tell whether the additional limitation of the claims – i.e., "adjacent a CDR in the immunoglobulin sequence" – is satisfied because the answer will change depending upon the limits of the CDRs.

Additionally, such an interpretation would also make the recitation “outside the Kabat and Chothia CDRs” superfluous. But, as discussed above, the prosecution history of the Queen patent indicates that the recitation was necessary to secure allowance over the prior art. Indeed, when faced with a rejection over Riechmann, Queen did **not** argue that “CDR” means Kabat or Chothia. Queen, rather, added the “outside the Kabat and Chothia CDRs” limitation in the application that issued as the Queen patent. Thus, such an interpretation is inconsistent with the file history.

Finally, as is clear from the discussion of the two earliest priority documents above, all references to CDRs were to Kabat CDRs, not Kabat or Chothia. Accordingly, even if the Office’s interpretation of CDRs were correct, the two earliest priority documents do not support the Office’s interpretation.³

Appellants arguments, however, were unavailing. A Final Rejection dated as mailed July 12, 2004, followed. The original appeal was taken from that Final Rejection. In that Final Rejection, the Office maintained its position, and alleged that it meant to argue Kabat or Chothia in the earlier March 2003 Action. The Office argued that

. . . dependent which of the definition of CDRs, Kabat or Chothia, is used in the humanized antibody, it would be routine in the art to determine which amino acids constitute the framework, or which amino acids are outside of or adjacent to the CDRs, since the amino acids of the Kabat or Chothia CDRs are well know in the art.

³ Notably, the Office relied upon the very same passage in the 975 application to support the Kabat **or** Chothia interpretation that it relied upon to support the Kabat **and** Chothia interpretation for the term “CDRs”— page 9, lines 1-5, of Application Serial No. 290,975, Evidence Appendix D.

(Final Rejection dated as mailed July 12, 2004, page 4.) The Office's analysis, however, focuses upon enablement, which is distinct from written description and definiteness. Appellants position is, and has been, that there is no written descriptive support for the limitation "outside the Kabat and Chothia CDRs" in the two earliest priority applications. The Office has not successfully countered this position with its strained interpretations of the term "CDRs;" there is no written descriptive support for either interpretation.

In the answer to Appellants' arguments designated as "C" in the present Office Action, the Office asserted that this limitation is met because **many** of the replaced amino acids are "inherently" outside both the CDRs as described by Kabat and the structural loop CDRs as described by Chothia et al. But this assertion is a misapplication of inherency.

To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'

In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). That **many** of the replaced residues were outside the Kabat and Chothia CDRs, thus, is insufficient to support a limitation requiring that **all** the replaced residues be outside the Kabat and Chothia CDRs. Most notably, as admitted by the Office at page 5 of the present Office Action, heavy chain residue 27 was disclosed as being replaced in the 975 application; heavy chain residue 27, however, is within the Chothia heavy chain CDR1 .

CONCLUSION

Appellants maintain that there is no support in the two earliest priority applications for at least three limitations recited in all claims of the Queen patent. Those limitations are:


1. “an affinity constant of at least 10^7 M^{-1} ,”
2. “no greater than about four-fold that of the donor immunoglobulin,” and
3. “outside the Kabat and Chothia CDRs.”

The absence of support for any one of these limitations in the two earliest priority applications precludes reliance on those applications for a reference date under 35 U.S.C. § 102(e)/103. *In re Wertheim*, 646 F.2d 527, 209 USPQ 554 (CCPA 1981). The rejection of claims 24-31 under 35 U.S.C. § 102(e)/103 over the Queen patent, thus, is inappropriate and should be reversed.

Respectfully submitted,

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CLAIMS APPENDIX

24. A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least 10^8 M^{-1} , wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside both the Kabat CDRs and the structural loop CDRs of the variable regions, wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, and each of said donor amino acids contributes to antigen binding as determined by X-ray crystallography.

25. A humanized immunoglobulin according to claim 24 which specifically binds to an antigen with an affinity in the range 10^8 - 10^{12} M^{-1} .

26. A humanized immunoglobulin according to claim 24, wherein the antigen is an IL-2 receptor.

27. A humanized immunoglobulin according to claim 24, wherein the donor immunoglobulin is the anti-CD4 T-cell receptor antibody.

28. A humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks

from human acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an effective antigen binding affinity, wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside both the Kabat CDRs and the structural loop CDRs of the variable regions, wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, and each of said donor amino acids contributes to antigen binding as determined by X-ray crystallography.

29. A humanized immunoglobulin according to claim 28 which specifically binds to an antigen with a binding affinity similar to that of said donor immunoglobulin.

30. A humanized immunoglobulin according to claim 28, wherein the antigen is a human CD3 T-cell receptor.

31. A humanized immunoglobulin according to claim 28, wherein the donor immunoglobulin is the anti-CD3 T-cell receptor antibody.

EVIDENCE APPENDIX

INDEX:

Evidence Appendix A – U.S. Patent No. 5,585,089 issued to Queen et al

The Queen patent was initially submitted with the Preliminary Amendment filed concurrently with the present application on May 1, 1997, and was relied upon by the Office in making the rejection being appealed in the Office Action dated as mailed November 16, 1998.

Evidence Appendix B⁴ -- Request for Reconsideration filed on May 24, 2000 and Appendix A attached thereto

The May 24, 2000 Request for Reconsideration was referenced as considered in the Final Rejection dated as mailed September 8, 2000.

Evidence Appendix C – Queen Application Serial No. 07/310,252

Relied upon by the Office during examination of the present application. See, for example, the Final Rejection dated as mailed May 28, 1999. It was submitted in the parent of the present application, Application Serial No. 08/303,569 (“the 569 application”), with a protest filed by the proprietors of the Queen patent on April 1, 1997. A copy of the protest, and the Office’s reference to same, is attached to this index. The 569 application was withdrawn from issuance for consideration of the protest.

Evidence Appendix D – Queen Application Serial No. 07/290,975

Relied upon by the Office during examination of the present application. See, for example, the Final Rejection dated as mailed May 28, 1999. It was submitted in the parent of the present application, the 569 application, with a protest filed by the proprietors of the Queen patent on April 1, 1997. A copy of the protest, and the Office’s reference to same, is attached to this index. The 569 application was withdrawn from issuance for consideration of the protest.

⁴ Entry of Evidence Appendix into the record was confirmed upon review of the Image File Wrapper for this application.

Evidence Appendix E -- Paper No. 7, Application Serial No. 07/634,278, filed December 19, 1990, attached as Exhibit 6 to the Supplemental Amendment filed March 17, 2003, page 7.

Arguments supported thereby acknowledged in the Office Action dated as mailed August 21, 2003. Resubmitted to Examiner Davis on February 10, 2005, for entry.

Evidence Appendix F -- Paper No. 6, Application Serial No. 07/634,278, filed December 19, 1990, attached as Exhibit 5 to the Supplemental Amendment filed March 17, 2003, page 1.

Arguments supported thereby acknowledged in the Office Action dated as mailed August 21, 2003. Resubmitted to Examiner Davis on February 10, 2005, for entry.

Evidence Appendix G⁵ -- Queen's European patent 451,216

Copy attached as Exhibit 1 to the Request for Reconsideration filed May 20, 2002. Acknowledged in the Advisory Action dated as mailed August 28, 2002.

Evidence Appendix H⁶ -- Request for Reconsideration filed May 20, 2002

The Request for Reconsideration filed May 20, 2002 was acknowledged by the Office in the Advisory Action dated as mailed August 28, 2002.

Evidence Appendix I⁷ -- Interlocutory decision in Opposition Proceedings for Queen European Patent

Copy attached as Exhibit 4 to the Request for Reconsideration filed May 20, 2002. Acknowledged in the Advisory Action dated as mailed August 28, 2002.

Evidence Appendix J⁸ -- Paper filed June 22, 2001 by Protein Design Labs in appeal of EP-B1 0451 216

⁵ Entry of Evidence Appendix into the record was confirmed upon review of the Image File Wrapper for this application.

⁶ Entry of Evidence Appendix into the record was confirmed upon review of the Image File Wrapper for this application.

⁷ Entry of Evidence Appendix into the record was confirmed upon review of the Image File Wrapper for this application.

⁸ Entry of Evidence Appendix into the record was confirmed upon review of the Image File Wrapper for this application.

Copy attached as Exhibit 5 to the Request for Reconsideration filed May 20, 2002. Acknowledged in the Advisory Action dated as mailed August 28, 2002.

Evidence Appendix K⁹ -- Paper filed July 13, 2001 by Protein Design Labs in EP 95 10 5609.2

Copy attached as Exhibit 6 to the Request for Reconsideration filed May 20, 2002. Acknowledged in the Advisory Action dated as mailed August 28, 2002.

Evidence Appendix L¹⁰ -- Supplemental Amendment filed March 17, 2003

Referenced in the Office Action dated as mailed August 21, 2003.

⁹ Entry of Evidence Appendix into the record was confirmed upon review of the Image File Wrapper for this application.

¹⁰ Entry of Evidence Appendix into the record was confirmed upon review of the Image File Wrapper for this application.

RELATED PROCEEDINGS APPENDIX

NONE